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Translating concepts of neural repair after stroke: Structural and functional targets for recovery

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Abstract

Stroke is among the commonest causes of adult disability worldwide, and its disease burden is shifting towards that of a long-term condition. Therefore, the development of approaches to enhance recovery and augment neural repair after stroke will be critical. Recovery after stroke involves complex interrelated systems of neural repair. There are changes in both structure (at the molecular, cellular, and tissue levels) and function (in terms of excitability, cortical maps, and networks) that occur spontaneously within the brain. Several approaches to augment neural repair through enhancing these changes are under study. These include identifying novel drug targets, implementing rehabilitation strategies, and developing new neurotechnologies. Each of these approaches has its own array of different proposed mechanisms. Current investigation has emphasized both cellular and circuit-based targets in both gray and white matter, including axon sprouting, dendritic branching, neurogenesis, axon preservation, remyelination, blood brain barrier integrity, blockade of extracellular inhibitory signals, alteration of excitability, and promotion of new brain cortical maps and networks. Herein, we review for clinicians recovery after stroke, basic elements of spontaneous neural repair, and ongoing work to augment neural repair. Future study requires alignment of basic, translational, and clinical research. The field continues to grow while becoming more clearly defined. As thrombolysis changed stroke care in the 1990s and thrombectomy in the 2010s, the augmentation of neural repair and recovery after stroke may revolutionize care for these patients in the coming decade.

Keywords

stroke; recovery; neural repair; translation

Introduction

Stroke is among the commonest causes of adult disability worldwide (GBD 2016 Stroke Collaborators, 2019; Murray & Lopez, 2013; Regenhardt, Bischoff et al., 2019). Furthermore,

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there has been an epidemiological shift of its disease burden towards that of a long-term condition, suggesting that the number of patients with stroke will continue to rise (Crichton, Bray, McKeivitt, Rudd, & Wolfe, 2016). Therefore, the development of approaches to enhance recovery and augment neural repair after stroke will be critical. Herein, we provide a narrative review for clinicians broadly summarizing recovery after stroke, basic elements of neural repair, and ongoing work to augment repair. To devise novel interventions, an understanding of the spontaneous repair processes that occur in the brain after stroke is essential. Ongoing work builds on mounting data to identify strategies to improve the brain's capacity to repair itself, through pharmacological, rehabilitative, and neurotechnological means.

Many factors make the clinical translation of therapies a challenging task. Stroke is a heterogeneous disease. Repair and recovery are highly dependent upon the brain regions involved (Minnerup et al., 2018) and the time point after stroke through a biphasic progression as damaged brain transitions from injury into repair (E. H. Lo, 2008). Interventions that target repair are unique compared to acute reperfusion and neuroprotection strategies. Those that target repair have a different timeline (weeks to months versus hours to days) and different target (augmenting the function of surviving tissue rather than saving dying tissue) (Cramer, 2018). Unlike acute therapies to “save” brain, repair-focused therapies emphasize repairing, replacing, and “re-wiring” damaged brain (i.e. plasticity) (Corbett, Nguemeni, & Gomez-Smith, 2014; Cramer et al., 2011; Regenhardt et al., 2017; Regenhardt et al., 2018). In the weeks to months after stroke, spontaneous changes are seen in areas surrounding the infarct and those with network connections to the infarct (Cramer & Chopp, 2000; Hermann & Chopp, 2012; Nudo, 2011; Overman & Carmichael, 2014). These changes are interrelated and occur at both the structural (molecular, cellular, and tissue) and functional levels (excitability, cortical maps, and networks).

At the level of the individual patient, recovery after stroke can be variable and difficult to predict (Ward, 2017). While both reflect functional improvement, a distinction should be made between compensation and true recovery (J. W. Krakauer, Carmichael, Corbett, & Wittenberg, 2012). Compensation is the use of alternative strategies to accomplish a task or goal, such as the use of the unaffected limb. In contrast, true recovery occurs through neural repair, when brain regions regain function or when undamaged brain regions are recruited to generate commands to the same muscles that were used before injury. Complicating our understanding of recovery, many early trials failed to measure true recovery directly and instead measured global outcomes.

Different symptoms after stroke, including motor weakness, aphasia, neglect, and apraxia, spontaneously recover at different rates (Cassidy, Lewis, & Gray, 1998; Desmond, Moroney, Sano, & Stern, 1996; Hier, Mondlock, & Caplan, 1983; Lazar et al., 2010; Nijboer, Kollen, & Kwakkel, 2013; Pedersen, Jorgensen, Nakayama, Raaschou, & Olsen, 1995; Sunderland, Tinson, & Bradley, 1994; Wade, Parker, & Langton Hewer, 1986). The most data exist for motor recovery as it is amenable to more objective measurement (Duncan, Goldstein, Matchar, Divine, & Feussner, 1992). The dominant predictive factor is the initial severity of impairment (Coupar, Pollock, Rowe, Weir, & Langhorne, 2012), where milder deficits

recover faster and achieve higher levels of function (Cramer, 2008). One classic study showed that arm function achieved maximum recovery in 95% of patients within 9 weeks (Nakayama, Jorgensen, Raaschou, & Olsen, 1994). More recently, the proportional recovery rule has been described for upper limb motor impairment: at 3 months, patients with mild to moderate initial impairments achieve approximately 70% of their maximum potential for recovery (Byblow, Stinear, Barber, Petoe, & Ackerley, 2015; J. W. Krakauer & Marshall, 2015; Prabhakaran et al., 2008; Winters, van Wegen, Daffertshofer, & Kwakkel, 2015; Zarahn et al., 2011). This “rule” has come under controversy recently (Hawe, Scott, & Dukelow, 2018; Hope et al., 2019; Senesh & Reinkensmeyer, 2019). Nevertheless, two themes hold for spontaneous recovery after stroke. First, most recovery occurs in the first weeks after stroke and involves stereotyped biological processes (as described below). Second, there is a substantial amount of individual variation in recovery after stroke that likely involves personal, genetic, and environmental factors. Ongoing research aims to identify other prognostic biomarkers, such as corticospinal tract lesion extent and prediction tools based on clinical variables; there has been progress predicting ultimate limb motor impairment, walking, and swallowing (Stinear, Smith, & Byblow, 2019).

Changes in structure: Repair at the molecular, cellular, and tissue levels

After stroke, there are spontaneous changes in both structure and function in the brain (Table 1, Figure 1). Repair refers to these collective changes if they lead to functional recovery (Krakauer, J.W., Carmichael, S.T., 2017). The distinction is important because it emphasizes that reorganization described in histological studies should not be considered repair unless the changes have functional consequences. The basic elements of structural changes were first described in animal models and involve both gray and white matter (Carmichael, 2016; Murphy & Corbett, 2009; Wahl & Schwab, 2014; Wieloch & Nikolich, 2006). Subsequently, humans have been found to have similar changes (Jin et al., 2006; Sanin, Heess, Kretschmar, & Schuller, 2013). These changes occur in areas connected to the infarcted area, including peri-infarct, ipsilateral brain, contralateral brain, and spinal cord (Benowitz & Carmichael, 2010; Murphy & Corbett, 2009; Overman & Carmichael, 2014; Starkey & Schwab, 2014). In preclinical models, the temporal and spatial ordering of these events is governed by alterations in gene expression. Cytokines, chemokines, growth factors, and other molecules, including SDF-1, Ang-1, Ang II, CCL2, LIF, TNFalpha, TGFbeta, NGF, GDF10, BDNF, and FGF-2, are secreted from activated astrocytes, microglia, and endothelial cells to initiate and govern these processes (Berry et al., 2005; Davis et al., 2019; Kahle & Bix, 2013; Klassen et al., 2003; Krakauer, J.W., Carmichael, S.T., 2017; Ohab & Carmichael, 2008; Regenhardt et al., 2013; Regenhardt, Bennion, & Sumners, 2014). Details of these pathways are beyond the scope of this review; however, we summarize these terms and others with references (Table 2). Interestingly, while post stroke brain resembles developing brain in many ways at the cellular and tissue levels, the regenerative and developmental transcriptomes are different (Cramer & Chopp, 2000; Li et al., 2010).

After infarction of gray matter, changes in axonal connections are initiated in the first week after stroke and persist for at least one month in the mouse (Carmichael, Wei, Rovainen, & Woolsey, 2001; Overman et al., 2012). There is evidence for axonal sprouting in humans as GAP43, highly involved in this process, is upregulated in the peri-infarct. Remaining

neurons in the peri-infarct can form robust new connections (Krakauer, J.W., Carmichael, S.T., 2017; Overman et al., 2012). These processes have been found distances away from the infarct in the mouse (Li et al., 2015; Overman et al., 2012) and nonhuman primate (Dancause et al., 2005). Furthermore, axonal sprouting is not simply a function of proximity, but of functionally linked brain regions (Li et al., 2015; Overman et al., 2012). There is an early induction transcriptome for axonal sprouting in the first week post stroke and a later maintenance transcriptome at 3 weeks (Li et al., 2010). Repair in gray matter likely also involves dendritic branching. Initially, there is a loss of dendritic spines in the peri-infarct during the first week after stroke in preclinical models (Brown, Wong, & Murphy, 2008; Mostany et al., 2010), reflecting a loss of synaptic connections. Subsequently, dendritic spines recover to premorbid levels and can even increase compared to controls. Branches remodel with retraction and growth that is maximal two weeks after infarct (Brown, Boyd, & Murphy, 2010).

Neurogenesis, gliogenesis, and angiogenesis may also play a role in repair. These processes involve the generation of new neurons, glia, and blood vessels, respectively. While there remains limited evidence for these processes in primates (Imayoshi et al., 2008; Lee & Thuret, 2018), progenitors from the subventricular zone (SVZ) can proliferate, migrate to the peri-infarct cortex, and mature into new neurons in response to ischemia in rodent models (Ekdahl, Kokaia, & Lindvall, 2009; Kernie & Parent, 2010; Ohab & Carmichael, 2008). Depending on the distance of the stroke from the SVZ, there is variable neuroblast migration with distant cortical sites having lower numbers (Ohab & Carmichael, 2008). Experimentally augmenting neurogenesis is associated with improved recovery (Leker et al., 2007; Ohab, Fleming, Blesch, & Carmichael, 2006; L. Wang, Zhang, Wang, Zhang, & Chopp, 2004), while inhibiting neurogenesis impairs recovery (Garcia, Doan, Imura, Bush, & Sofroniew, 2004; Imayoshi et al., 2008). Recently, SVZ-derived neurons have been shown to synaptically integrate into peri-infarct cortex, in a mouse model, in a manner that is activity-dependent and sensitive to modulation (Liang et al., 2019).

Angiogenesis is also hypothesized to play a role in repair after stroke (Arai, Jin, Navaratna, & Lo, 2009). It has been shown to be triggered by experimental ischemia in the brain (Fan & Yang, 2007) and occurs primarily in the peri-infarct, although it also occurs in other regions including the contralesional cortex (Ergul, Alhusban, & Fagan, 2012; Liu et al., 2014). Endothelial cell proliferation may occur as early as 12 hours after ischemia and persist for several weeks in mice (Hayashi, Noshita, Sugawara, & Chan, 2003; Marti et al., 2000). Growth factors and chemokines are secreted (discussed subsequently), leading to new microvessels with pericytes and smooth muscle cells. Human autopsy studies confirmed angiogenesis occurs after stroke and the extent of which correlates with survival (Krupinski, Kaluza, Kumar, Kumar, & Wang, 1994).

In addition to gray matter, white matter also undergoes repair and has been under-studied as a target (Das, Regenhardt, Feske, & Gurol, 2019; Regenhardt, Das et al., 2019). Twenty-five percent of strokes involve exclusively white matter (Regenhardt, Das, Lo, & Caplan, 2018). Furthermore, white matter is involved to some degree in most other strokes, and its injury accounts for the second leading cause of dementia (Sozmen et al., 2016). When white matter undergoes ischemia, there is primary injury to axons involving calcium signaling and

proteolysis. In the subacute period after stroke, a second progressive phase of injury occurs affecting axons that survive the initial infarct. Degeneration of axons occurs through contact with glia and altered energy metabolism in preclinical models (Hinman, 2014). A third degenerative/regenerative phase may further contribute involving anterograde Wallerian degeneration and retrograde signals to the soma that may influence axonal sprouting and reconnection (Hinman, 2014).

Injury to myelin also occurs in stroke, leaving axons dysfunctional and vulnerable. However, endogenous repair mechanisms are initiated in the mouse involving oligodendrocyte precursor cells (OPCs) and remyelination (Sozmen, Kolekar, Havton, & Carmichael, 2009). Much of our understanding of OPC function comes from models of multiple sclerosis (MS), showing that there are cues for resident OPCs to proliferate, migrate, and differentiate into myelinating oligodendrocytes (Franklin, 2002; Shindo et al., 2016; Sozmen & Carmichael, 2014). In the last several years, models have been developed, including cell, tissue, and whole animal platforms, to study white matter recovery after stroke, (Arai & Lo, 2009; Regenhardt et al., 2018).

Changes in function: Repair in terms of excitability, brain cortical maps, and networks

In addition to structural changes, there are also changes in neural function including excitability and changes in brain networks (Carmichael, 2012). Acutely, surviving brain becomes excitable relative to baseline. Indeed, blocking this excitotoxicity is a target for neuroprotection. In the mouse, there is a three-day period with excess excitation (Clarkson, Huang, Macisaac, Mody, & Carmichael, 2010); glutamate is excitotoxic and contributes to cell death, while GABA can counteract this toxicity (Lai, Zhang, & Wang, 2014). After this three-day period in mouse models (unclear timeline in humans), this is reversed and there is excess inhibition in the recovery phase, through an altered GABA vs glutamate balance when reactive astrocytes downregulate their GABA uptake systems (Carmichael, 2012). Interestingly, interventions that reduce the pathologic inhibitory tone in this phase can cause downstream beneficial changes in structure (J. L. Chen et al., 2011). It has been proposed that changes in excitability regulate growth factors and cytokines perhaps through epigenetic mechanisms (Felling & Song, 2015). Furthermore, preclinical models have shown reducing inhibition can lead to expanded and less-specific receptive fields (Alia et al., 2016; Winship & Murphy, 2008), enhanced long term potentiation (Hagemann, Redecker, Neumann-Haefelin, Freund, & Witte, 1998), and remapping of sensorimotor functions to surviving cortex in both hemispheres (Que et al., 1999; Takatsuru et al., 2009).

Experimental methods to reduce inhibition include increasing glutamate-AMPA signaling, further decreasing phasic GABA (synaptic) signaling, and decreasing tonic GABA (extrasynaptic) signaling (Murphy & Corbett, 2009). Increasing glutamate-AMPA signaling has been associated with improved recovery in a mouse model probably through downstream induction of BDNF (Clarkson et al., 2011). In addition, phasic GABA signaling has been shown to be spontaneously reduced in the first few weeks after stroke (Neumann-Haefelin, Hagemann, & Witte, 1995). This reduction can increase the likelihood of long-term potentiation (Hagemann et al., 1998). GABA_A receptors are downregulated (Que et al., 1999; Schiene et al., 1996) and the density of inhibitory interneurons is reduced after stroke

(Alia et al., 2016; Zeiler et al., 2013). In contrast, tonic GABA signaling has been shown to be increased after stroke in the mouse, through extrasynaptic GABA_A receptor signaling (Clarkson et al., 2010; Lake et al., 2015). This increased tonic inhibitory signaling persists for one month post stroke (Carmichael, 2012). When this is reversed with a GABA_A receptor inverse agonist, motor outcomes were improved in rodents (Clarkson et al., 2010; Neumann-Haefelin et al., 1995). Interactions between excitatory pyramidal neurons and inhibitory interneurons are complex, and this complexity likely increases after stroke (Clarkson, 2012). Strategies to reduce inhibition in human patients are being explored (discussed subsequently).

After stroke, there are also changes in cortical map representations and brain networks (Cramer, Moore, Finklestein, & Rosen, 2000; Ward & Cohen, 2004; Weiller, Ramsay, Wise, Friston, & Frackowiak, 1993). In non-human primate studies, infarcts that lead to a deficit in hand use are accompanied by a reduction in the cortical representation of the digit adjacent to the lesion (Nudo & Milliken, 1996). In humans, there are important network interactions after a single unilateral supratentorial stroke, where multiple brain areas are affected both in ipsilateral (Burke Quinlan et al., 2015; Carter et al., 2010; Grefkes et al., 2008; Grefkes & Fink, 2011; Sharma, Baron, & Rowe, 2009) and contralateral regions (Murase, Duque, Mazzocchio, & Cohen, 2004). There is increasing evidence that the contralateral hemisphere may play an adaptive role, especially in the subacute phase after stroke (Dodd, Nair, & Prabhakaran, 2017), and larger strokes employ more contralateral hemisphere (Heiss & Thiel, 2006; Netz, Lammers, & Homberg, 1997; Turton, Wroe, Trepte, Fraser, & Lemon, 1996). However, there is significant inter-patient variability, mechanistic details have yet to be established, and debate continues about a role for inhibiting contralateral hyperexcitability (Buetefisch, 2015; Dodd et al., 2017). Several approaches to augment repair, through enhancing these changes in structure and function, are under study. These include identifying novel drug targets, implementing rehabilitation strategies, and developing new neurotechnologies (Table 3). Each of these approaches has its own array of different proposed mechanisms.

Gray matter targets: Axon sprouting, dendritic branching, and neurogenesis

For gray matter stroke, several targets are under study. One promising agent, inosine, has been shown to increase axon growth and improve recovery in preclinical models. It promotes axonal sprouting, including into the corticospinal tract (Zai et al., 2009) by stimulating axonal growth programs (P. Chen, Goldberg, Kolb, Lanser, & Benowitz, 2002; Zai et al., 2009). Interestingly, inosine also augments the effects of anti-NogoA antibody (discussed subsequently) (Zai et al., 2011). Phosphodiesterase inhibitors may also have a role by blocking the degradation of cAMP and cGMP. cAMP stimulates cAMP response element-binding protein (CREB), which in turn regulates BDNF and axonal outgrowth (Clarkson, Parker, Nilsson, Walker, & Gowing, 2015; Xu, Zhang, & O'Donnell, 2011). PDE4 inhibitors have been shown to enhance motor performance when paired with rehabilitation in rats (MacDonald et al., 2007). In addition, the PDE5 inhibitor, Sildenafil, and PDE3 inhibitor, Cilostazol, are FDA approved agents that are under study (Krakauer, J.W., Carmichael, S.T., 2017). CCR5 blockade is another potential target in the translational pipeline. Involved in inflammatory processes post stroke, its blockade in a

mouse model prevented the initial loss of dendritic spines and promoted recovery (Joy, Zhou, Cai, Silva, & Carmichael, 2015). A cohort of stroke patients with a loss of function mutation for CCR5 showed greater recovery of neurological function (Joy et al., 2019). Another agent under investigation is cerebrolysin, a proprietary mixture of amino acids and peptides from pig brain (Harrer, Melnizky, & Wagner, 1972). It may stimulate neurogenesis through specific effects on neural progenitor cells involving the sonic hedgehog pathway (L. Zhang et al., 2013). In the CARS clinical trial, 21 days of treatment in addition to rehabilitation, starting 24-72 hours after stroke onset, showed promise (Muresanu et al., 2016). However, this was a small, exploratory study that has yet to be replicated.

As discussed above, growth factors are highly involved in repair and may serve as therapeutic targets (Finklestein et al., 1990; Lanfranchi et al., 2011). Examples include FGF-2 (Berry et al., 2005; Kawamata et al., 1997), BDNF (Schabitz et al., 2004), VEGF (Z. G. Zhang et al., 2000), EPO (Tsai et al., 2006; L. Wang, Zhang, Wang, Zhang, & Chopp, 2004), G-CSF (Schneider et al., 2007), and GDF10 (Li et al., 2015). EPO shows some promise as it was shown in the BETAS study to be safe in humans (Cramer et al., 2010). Unfortunately, the REGENESIS study was terminated early likely given significant differences in rehabilitation practice and lack of statistical power (Cramer, Hill, & REGENESIS-LED Investigators, 2014). The AXIS study showed G-CSF was safe in humans (Schabitz et al., 2010), however AXIS 2 showed no benefit compared to placebo (Ringelstein et al., 2013). GDF10 is currently under study given it is highly upregulated in the regenerative transcriptome in peri-infarct neurons, including in humans, and has been shown to promote functionally useful axonal sprouting (Li et al., 2015). A primary concern for many growth factors is off target effects, prompting exploration of approaches for local delivery (Krakauer, J.W., Carmichael, S.T., 2017).

Stem cells offer another potential option to promote repair (Azad, Veeravagu, & Steinberg, 2016). Cell therapies may stimulate endogenous repair processes, possibly replace damaged tissue, or reduce secondary injury events (Krakauer, J.W., Carmichael, S.T., 2017). Preclinical studies and phase I clinical trials show promise (Kalladka et al., 2016; Steinberg et al., 2016). In addition to stimulating endogenous cells, there are two main classes of exogenous stem cells: embryonic and induced pluripotent cells as well as adult-derived cells. Embryonic and induced pluripotent stem cells can be differentiated into neural stem cells that can become neurons and glia. While some preclinical studies suggest they can differentiate into neurons and integrate into circuitry (Kelly et al., 2004; Park, Teng, & Snyder, 2002; Tornero et al., 2013), they more likely exert benefit through stimulating endogenous processes rather than replacing damaged brain since most transplanted cells die (Barker, Gotz, & Parmar, 2018; Lemmens & Steinberg, 2013; J. Zhang & Chopp, 2013).

In contrast, adult-derived stem cells, usually from bone marrow or adipose, do not form neurons or glia *in vivo*. Most commonly, these are mesenchymal stem cells, which can produce growth factors and extracellular matrix proteins. While they are often trapped in the lungs, liver, and spleen (Boltze et al., 2015; Hicks & Jolkkonen, 2009), they exert effects on the immune system that may mediate repair in preclinical models (Boltze et al., 2015; Eckert et al., 2013). A meta-analysis of preclinical mesenchymal stem cell transplantation found large effect sizes, consistent across route of administration (Vu, Xie, Eckert, Zhao, &

Cramer, 2014). Clinical trials suggest they are safe, and there are trends for improvement (Kalladka et al., 2016; Steinberg et al., 2016). One study showed that post-mitotic human neuron-like cells derived from human testicular germ cell tumor could be feasibly implanted into humans (Kondziolka et al., 2000; Kondziolka et al., 2005). The more recent MASTERS trial showed that allogenic bone marrow-derived cells modulate the immune system, but do not likely enter the brain (Hess et al., 2017). Many questions about stem cells remain (Savitz, Cramer, Wechsler, & STEPS 3 Consortium, 2014): When to administer? Which cells and how many? Autologous vs allogenic? What route of administration: intravenous, intra-arterial, or surgical (*i.e.* Intraparenchymal)? Are scaffolding gels beneficial? For these reasons, further data are needed to determine efficacy and safety; patients seeking these therapies should be referred to academic centers conducting randomized controlled trials.

White matter targets: Axon preservation, remyelination, and blood brain barrier

In addition to gray matter targets, therapies to prevent axonal degeneration, aid remyelination, and stabilize the blood-brain barrier (BBB) have been examined after white matter stroke (Xiao & Hinman, 2016). A mouse model demonstrated that the volume of white matter infarcts enlarged over the first month (Sozmen et al., 2009). Studies in humans have also demonstrated that white matter infarcts can grow over time by serial imaging (Gouw et al., 2008). While the clinical significance of this slow stroke growth is unknown, it may prove a viable therapeutic target. Another mouse model of chronic white matter ischemia has demonstrated that injured axons show elongation of nodes and paranodes (Reimer et al., 2011), which slows conduction velocity (Babbs & Shi, 2013). The peri-infarct was examined in human white matter strokes, and axons up to 150% of the infarct diameter away showed disorganization of nodes and paranodes, despite maintaining intact structure of neurofilaments (Hinman, Lee, Tung, Vinters, & Carmichael, 2015).

There are three phases of axon injury and repair after stroke: primary injury, secondary progressive injury, and tertiary degeneration/regeneration (Hinman, 2014). In the secondary phase, axons swell and form retraction bulbs in preclinical models (Taguohi et al., 1989; Q. Zhang et al., 2012). These dying axons release signals that cause reactive astrocytes and microglia to respond within days to weeks (Block, Dihne, & Loos, 2005; J. Zhang, Zhang, Xing, Liang, & Zeng, 2012). Furthermore, when axons are disconnected from energy from the soma, MCT-1 from oligodendrocytes may serve as an alternative source through the transfer of lactate. Augmentation of the MCT-1 pathway may have therapeutic potential (Hinman, 2014; Rinholm et al., 2011). In the tertiary degeneration/regeneration phase, distal portions of axons undergo anterograde Wallerian degeneration mediated by NMNAT1 and retrograde signals to the cortical soma may involve degeneration/regeneration mediated by DLK and STAT3 (Hinman, 2014; Hinman et al., 2015). Manipulating these pathways to limit degeneration and promote regeneration may also prove fruitful.

Another proposed target in white matter is remyelination. It has been hypothesized that the aforementioned slow white matter stroke growth may occur secondary to eventual loss of vulnerable hypomyelinated peri-infarct axons in the mouse. Indeed, myelin loss was found to exceed axon damage in this model (Sozmen et al., 2009). Perhaps the disorganization of nodes and paranodes in human peri-infarct reflects a loss of normal cell-cell adhesion and

signaling between axons and oligodendrocytes (Hinman et al., 2015). Remyelination has long been the Holy Grail for many neurologic diseases like MS. The obvious difference comparing MS to stroke is that the latter involves death of all cell types. Also, given there is likely a critical period after stroke, therapies may be high dose and short duration, minimizing off target effects. OPCs are delicate and highly susceptible to ischemia, have only a limited capacity to differentiate, and require proximity to the axons that they may remyelinate. Methods to increase OPC proliferation and differentiation, including the use of exogenous stem cells, are being explored (Shindo et al., 2016; Xiao & Hinman, 2016).

Other theoretical targets may exist in both white and gray matter. There may be approaches to manipulate microglia to promote a repair-oriented inflammatory milieu. In several mouse models of white matter stroke, microglia/macrophages were found near injured axons at day one, and increased until day seven while OPCs decreased (Hayakawa, Wang, & Lo, 2016; Hayakawa et al., 2016; Sozmen et al., 2009). Microglia have the potential to be detrimental in stroke by producing pro-inflammatory cytokines and reactive oxygen/nitrogen species (Hanisch & Kettenmann, 2007; Raivich & Banati, 2004; Regenhardt et al., 2014; Rosenzweig & Carmichael, 2015; J. Wang & Dore, 2007), impairing glutamate uptake (Arai & Lo, 2009; Takahashi, Giuliani, Power, Imai, & Yong, 2003), triggering excitotoxic oligodendrocyte death (Arai & Lo, 2009; Takahashi et al., 2003), and ingesting OPCs (Hughes, Kang, Fukaya, & Bergles, 2013). However, microglia can also produce anti-inflammatory cytokines and growth factors (Turrin & Rivest, 2006; J. Wang & Dore, 2007), secrete agents to promote oligodendrogenesis (Butovsky, Landa et al., 2006; Butovsky, Ziv et al., 2006; Mason et al., 2000; Mason, Suzuki, Chaplin, & Matsushima, 2001; Miron et al., 2013; Tanaka, Murakami, Bando, & Yoshida, 2013), and support remyelination through the phagocytosis of myelin debris and apoptotic cells (Olah et al., 2012; Turrin & Rivest, 2006; J. Wang & Dore, 2007). By inhibiting TLR4 signaling in microglia/macrophages, phagocytosis of OPCs was decreased and myelination was improved at day 14 after stroke in a mouse model (Hayakawa et al., 2016; Hayakawa et al., 2016). Another target may be the BBB, made up of tight junctions, multicellular interactions, and transcellular transport systems. It is hypothesized that failure of endothelial cells and pericytes to maintain this system underlies white matter injury. It may be possible to restore metabolic function to endothelial cells and promote pericyte proliferation with agents that do not have to cross the BBB (Xiao & Hinman, 2016).

Glial scar and blocking extracellular inhibitory signals

Another approach to augmenting repair is the modulation of glial scarring, relevant in both gray and white matter. After the acute phase, astrocytes and OPCs synergize with the inflammatory response and play a key role in the formation of glial scar. Scar is hypothesized to be beneficial acutely by sealing off the area of injury and closing the BBB. In preclinical models, reactive astrogliosis can be beneficial in certain circumstances (Hayakawa, Pham, Katusic, Arai, & Lo, 2012; Sofroniew, 2009), and without reactive astrocytes there is increased lesion size and inflammation acutely (Sofroniew, 2012). Chronically, however, several cell surface and extracellular matrix proteins have been shown to inhibit axon growth and impair the ability of oligodendrocytes to myelinate axons (Giger et al., 2008).

There are several inhibitory signals that may affect repair after stroke including myelin-associated proteins, extracellular matrix proteins, and growth cone inhibitors. Of the myelin-associated proteins, NogoA, MAG, and MOBP have undergone the most study (Cramer et al., 2013). In one model, rats administered anti-NogoA antibodies recovered motor control after sensorimotor cortex ablation with corticospinal tract sprouting across the midline into the denervated spinal hemicord, leading to a somatotopic anatomical and functional side switch (Lindau et al., 2014). Similar findings were seen with Nogo receptor 1 (NgR1) blockade in a mouse model of middle cerebral artery occlusion (Takase, Kurihara, Yokoyama, Kawahara, & Takei, 2017). Recently, NgR1 blockade was shown to overcome remyelination failure after white matter stroke to stimulate functional recovery in mice (Sozmen et al., 2016). Safety in humans has already been demonstrated (Meininger et al., 2014; Wahl & Schwab, 2014). Chondroitin sulfate proteoglycans (CSPs) are an example of extracellular matrix proteins. These mediate the inhibitory properties of perineuronal nets, which are responsible for synapse stabilization. In doing this, CSPs block axon growth. In a preclinical model, cortical infarcts lead to a reduced density of perineuronal nets in the peri-infarct, possibly allowing increased plasticity (Alia et al., 2016). Chondroitinase ABC can inactivate CSPs and perineuronal nets, thereby allowing additional plasticity (Pizzorusso et al., 2002) and restoring motor function (Gherardini, Gennaro, & Pizzorusso, 2015). Growth cone inhibitors, such as semaphorins and ephrins, inhibit the axonal growth cone, which is an extension of a regenerating neurite seeking its synaptic target. In the peri-infarct, ephrin-A5 is induced in astrocytes and has been shown to inhibit axonal sprouting. Blocking this pathway has been shown to promote recovery in a mouse model (Overman et al., 2012).

Altering excitability

Another potential mechanism to augment neural repair is through the alteration of excitability and neurotransmitters. As discussed above, animal models have demonstrated this proof of principle through experiments that decrease pathologic inhibitory tone. Since the 1980s, several FDA-approved drugs have been studied in humans. One of the first agents studied to augment recovery after stroke were amphetamines. They were shown to increase noradrenergic function and aid recovery after cortex ablation in a rat model when paired with rehabilitative therapy (Feeney, Gonzalez, & Law, 1982). Unfortunately, amphetamines failed to augment repair in clinical trials, possibly given lack of pairing with intense rehab, small heterogeneous studies, and concerns for adverse effects (Goldstein, 2009; Martinsson, Hardemark, & Wahlgren, 2003). The STARS trial showed no benefit of amphetamine twice weekly for 5 weeks when patients were enrolled 5-10 days post stroke (Gladstone et al., 2006).

SSRIs have been the subject of recent attention, with the most data for fluoxetine. Several small trials showed positive effects on motor recovery (Mikami et al., 2014; Robinson et al., 2008). In the FLAME trial (Chollet et al., 2011), patients were enrolled within 10 days of stroke and treated for 3 months showing reduced motor impairment (Fugl-Meyer) and disability (modified Rankin). However, the larger FOCUS trial (FOCUS Trial Collaboration, 2019) did not replicate the reduced disability at 6 months, but the more sensitive impairment endpoint was not examined and the patients enrolled were heterogeneous with all levels of initial impairment. Preclinical models propose several possible mechanisms. It is

hypothesized that treatment reinstates a critical period of plasticity in rats by decreasing inhibition through reducing extracellular GABA (Maya Vetencourt et al., 2008). Another study showed fluoxetine prolonged but did not reinstate this critical period in mice through a reduction of inhibitory interneuron expression in intact cortex (K. L. Ng et al., 2015). In human primary motor cortex slices, fluoxetine reduced the inhibitory tone through suppression of layer II-III monosynaptic excitatory connections from pyramidal neurons to inhibitory interneurons (Komlosi et al., 2012). Interestingly, SSRIs have been shown to activate CREB (Mostert, Koch, Heerings, Heersema, & De Keyser, 2008). In addition to regulating BDNF and axonal outgrowth (Clarkson et al., 2015; Xu et al., 2011), CREB activates genes that enhance excitability (Dong et al., 2006; Han et al., 2006), long term potentiation (Wu, Zhou, & Xiong, 2007), cortical re-mapping, and recovery in animal models (Caracciolo et al., 2018), exemplifying the interplay between structural and functional changes. Indeed, other pharmacological means of inducing CREB may be possible (Caracciolo et al., 2018; Krakauer, J.W., Carmichael, S.T., 2017).

Zolpidem has also been examined for potential effects after stroke. Indeed, it showed improved recovery in a mouse model (Hui et al., 2016), and there are case reports of stroke patients with improved language, cognitive, and motor function (Cohen, Chaaban, & Habert, 2004; Hall et al., 2010). Zolpidem is believed to work through reducing tonic GABA_A inhibition at high levels. In addition, there is an ongoing trial using an alpha 5 GABA antagonist (RESTORE Collaborators, 2018). L-dopa has also shown some promise in recovery, though perhaps through reward-based mechanisms. One small randomized, placebo-controlled trial of 53 patients enrolled within 6 months of stroke showed that it resulted in mild improvements in motor function (Scheidtmann, Fries, Muller, & Koenig, 2001). However, other trials including DARS, have failed to replicate this (Bhakta et al., 2014; Ford et al., 2019; Lokk, Salman Roghani, & Delbari, 2011). In addition to agents that may decrease inhibition, there are also agents that may worsen it. While this topic is not commonly discussed on neurology units and wards, careful attention should be paid to agents that could be maladaptive for recovery. For example, diazepam and haloperidol have been shown to have negative effects on recovery (Dombovy, 2004; Feeney et al., 1982; Hovda & Feeney, 1985).

In addition to pharmacologic means, transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) are under study to stimulate pathologically inhibited cortex. TMS involves the placement of a stimulator on the scalp that issues magnetic pulses to induce action potentials in cortical neurons. A Cochrane review was inconclusive, but a more recent meta-analysis of arm motor recovery showed promising results (Hao, Wang, Zeng, & Liu, 2013; Hsu, Cheng, Liao, Lee, & Lin, 2012). High frequencies (5-20 Hz) are used to increase cortical excitability (Rossi, Hallett, Rossini, Pascual-Leone, & Safety of TMS Consensus Group, 2009). Mounting evidence suggests high frequency to ipsilateral motor cortex may improve hand function (Khedr, Ahmed, Fathy, & Rothwell, 2005; Y. H. Kim et al., 2006). Low frequencies (1 Hz), in contrast, are used to decrease cortical excitability with the aim to treat distant cortical regions (Dayan & Cohen, 2011; Liew, Santarnecchi, Buch, & Cohen, 2014; Naeser et al., 2005). Small studies have shown low frequency over the contralesional motor cortex may improve hand function after stroke (Fregni et al., 2006; Kobayashi, Hutchinson, Theoret, Schlaug, & Pascual-

Leone, 2004; Nowak et al., 2008; Takeuchi, Chuma, Matsuo, Watanabe, & Ikoma, 2005). Another noninvasive approach to alter excitability utilizes tDCS. With this modality, DC current is supplied to the cortex via a scalp electrode. In contrast to TMS, tDCS does not cause action potentials but does alter resting membrane potentials (Hummel et al., 2005; Webster, Celnik, & Cohen, 2006). Early small studies suggest benefits in stroke recovery (Hummel et al., 2005; Hummel & Cohen, 2005). Through anodal stimulation, excitability can be increased; through cathodal stimulation, it can be decreased. A recent study showed enthusiasm for anodal tDCS to augment post-stroke swallowing function (Suntrup-Krueger et al., 2018). Interestingly, tDCS has been shown to induce CREB (Podda et al., 2016). Other approaches to stimulation are being explored, including work by Sabel *et al.* with transorbital stimulation (Fedorov et al., 2010; Sabel, Hamid, Borrmann, Speck, & Antal, 2019).

More invasive modalities of stimulation, including deep brain stimulation (DBS), epidural electrical stimulation, and vagal nerve stimulation, have been explored to a lesser extent. DBS has been well-established as a safe and effective treatment for movement disorders such as Parkinson's disease. For stroke patients, DBS has been used to treat a variety of maladaptive consequences of stroke including neuropathic pain and dystonia. Only a few case reports have used DBS to enhance motor recovery (Elias, Namasivayam, & Lozano, 2018). A trial evaluating epidural stimulation combined with rehabilitation did not show an effect (Levy et al., 2016). Vagal nerve stimulation (VNS) has also been explored. Preclinical studies show that VNS enhances structural plasticity in motor networks (Meyers et al., 2018). A recent clinical trial of VNS paired with rehabilitation demonstrated safety and feasibility in humans (Dawson et al., 2016).

Promoting new brain cortical maps and networks

Macro-level changes in cortical maps and networks involve underlying changes in excitability and structure. Interestingly, they don't always correlate temporally with behavioral recovery, leading some to question their role in repair (Krakauer, J.W., Carmichael, S.T., 2017). Translational approaches using rehabilitation and other neurotechnologies, many of which are incompletely understood, are believed to work through these mechanisms. The neurobiology of rehabilitation, including physical, occupational, and speech therapy, is only now becoming elucidated (L. Wang, Conner, Nagahara, & Tuszynski, 2016). The goals of rehabilitation are to enhance recovery, aid in adaptation to loss of neurologic function, and to continue preventative efforts to reduce recurrent stroke (Caplan, 2016). Several studies have shown that interdisciplinary stroke rehabilitation improves functional outcomes. As there is great heterogeneity in stroke symptoms, studies examining the effects of rehabilitation have measured different endpoints, including hemiplegic gait (Colborne, Olney, & Griffin, 1993; da Cunha et al., 2002; M. F. Ng, Tong, & Li, 2008), upper extremity function (Nakayama et al., 1994), aphasia (Shewan & Kertesz, 1984), and spatial neglect (Halligan & Marshall, 1994). A large meta-analysis collating studies from 1960-1990 including >3700 patients with hemiparesis showed that the average patient who took part in a rehabilitation program had better functional performance than 65% of patients in control groups (Ottenbacher & Jannell, 1993). There were greater effects of early treatment, and young patients did better than old.

Indeed, there is growing evidence suggesting that greater amount, duration, and intensity of activity based therapy improves outcomes in humans (Bhogal, Teasell, & Speechley, 2003; Cauraugh, Naik, Lodha, Coombes, & Summers, 2011; Galvin, Murphy, Cusack, & Stokes, 2008; Galvin, Cusack, O'Grady, Murphy, & Stokes, 2011; Kwakkel, Wagenaar, Twisk, Lankhorst, & Koetsier, 1999; Kwakkel et al., 2004; Legg, Langhorne, & Outpatient Service Trialists, 2004; Van Peppen et al., 2004). Another meta-analysis showed that the amount of therapy had positive influence on outcomes (Lohse, Lang, & Boyd, 2014). However, many patients don't receive maximal therapy in clinical practice (Bernhardt, Dewey, Thrift, & Donnan, 2004; Bernhardt, Chan, Nicola, & Collier, 2007; Kimberley, Samargia, Moore, Shakya, & Lang, 2010; Lang et al., 2009; Wade, Skilbeck, Hower, & Wood, 1984).

Interestingly, well controlled animal studies show that the number of forelimb reaches must exceed a certain threshold before an effect on recovery is observed (MacLellan et al., 2011). Parenthetically, the number of repetitive movements in animals needed to induce plasticity is orders of magnitude greater than those observed in humans in current clinical practice. There is also evidence to support a critical time period of rehabilitation therapy. One rat model demonstrated that motor training of the forelimb starting 30 days post stroke had little improvement compared to those that underwent earlier training (Biernaskie, Chernenko, & Corbett, 2004). While not well defined in humans (Zeiler, 2019), animal models point to a time-limited period of heightened plasticity after stroke (Zeiler et al., 2016). Extensive reach training in a rodent model was not able to promote recovery when started late at 7 days. However, in the same model, when a second stroke was induced two days later, recovery was substantially improved (Zeiler et al., 2016). Two strokes are not likely better than one, but this adds to evidence that additional ischemia may re-open a window for repair.

Several studies support the use of intense training that focuses on reducing impairment in the first weeks to take advantage of biological repair (J. W. Krakauer et al., 2012). However, as with pharmacologic interventions, there is the theoretical risk of rehabilitative efforts having detrimental effects if they are too early or too intense, as demonstrated in the AVERT trial (AVERT Trial Collaboration group, 2015). Indeed, certain behaviors can have detrimental effects. The compensatory use of the contralesional forelimb may impair recovery of the affected limb (Allred, Maldonado, Hsu And, & Jones, 2005), possibly through aberrant synaptogenesis in the peri-stroke cortex (S. Y. Kim et al., 2015). As behaviors, drugs, and their combination may take advantage of post stroke plasticity in both positive and negative ways, trials should be conducted with caution.

In addition to traditional physical therapy, several advanced therapies are gaining traction in clinical practice and are the focus of ongoing research. These include activity based therapies, sensory stimulation, telerehabilitation, and robot-based therapies (Cramer et al., 2019; Johansson, Lindgren, Widner, Wiklund, & Johansson, 1993; Lin, Finklestein, & Cramer, 2018). Constraint-induced movement therapy (CIMT) is an example of an activity based therapy that involves overcoming learned disuse of the stroke-affected limb by preventing use of the unaffected limb and forcing use of the affected (Taub, Uswatte, Mark, & Morris, 2006). The phase 3 EXCITE study showed that improvements after CIMT persist for at least 1 year (Wolf et al., 2006). Sensory stimulation is another therapy with a growing body of literature. Repetitive sensorimotor training involves rocking movements performed by the affected arm; one study showed improvement that persisted at 5-year follow-up (Feys

et al., 2004). Passive arm movement prior to active motor therapy may be superior to active motor therapy alone, possibly by balancing cortical excitability (Stinear, Barber, Coxon, Fleming, & Byblow, 2008). Neglect is also improved by many different sensory inputs (musical, optokinetic, neck proprioceptive, vestibular, and somatosensory) (Kerkhoff, 2003; Teasell & Kalra, 2004).

With advancing technology, telerehabilitation offers promise to increase access to therapy; it was recently shown noninferior to traditional in-clinic therapy (Cramer et al., 2019). Furthermore, robot-based therapies are becoming available though they are not often implemented clinically. Robots have been developed as tools to enhance post-stroke recovery (Hogan & Krebs, 2011; Krebs & Hogan, 2012), with numerous different robotic systems (Veerbeek, Langbroek-Amersfoort, van Wegen, Meskers, & Kwakkel, 2017; Volpe et al., 2009). A multicenter study showed that robot-assisted therapy was superior to usual physical therapy in reducing both upper extremity impairment and improving quality of life. The trial did not show benefits when compared to dose-matched intensive physical therapy (A. C. Lo et al., 2010), however high dose therapy involves thousands of repetitions and is thus not feasible routinely without the use of robotics. Furthermore, robots offer novel methods to measure effects of therapy and approaches can be personalized.

There are also several cognitive and behavioral strategies that may be implemented that synergize with motor rehabilitation. Some examples include cognitive rehearsal (Page, Levine, & Leonard, 2007), observing others perform a task (Celnik, Webster, Glasser, & Cohen, 2008), mirror visual feedback to overcome hemi-inattention (Ramachandran & Altschuler, 2009), real time neural feedback with fMRI (Berman, Horovitz, Venkataraman, & Hallett, 2012; Sitaram et al., 2012; Sulzer et al., 2013), and virtual reality (Fasotti & van Kessel, 2013). While there have been promising small pilot trials of virtual and augmented reality for stroke patients, larger trials and meta-analyses have not shown it to be more effective than conventional rehabilitation (Laver et al., 2017).

Brain-computer interfaces (BCIs) may afford both assistive and rehabilitation benefits after stroke. BCIs translate central nervous system signals into command signals for a technological device. For stroke rehabilitation, the underlying hypothesis is that by training patients to produce more normal brain activity patterns through feedback reinforcement, neuroplasticity mechanisms become engaged to allow for restoration of native neurologic function. A 2013 study showed that patients who underwent EEG-BCI training with an upper extremity orthosis showed significantly improved motor function. Perhaps most exciting, these improvements were correlated with adaptive changes in neural activity patterns on fMRI (Ramos-Murguialday et al., 2013). Another recent study demonstrated at-home use of an EEG-driven exoskeleton to open and close the affected hand from signals in the contralesional hemisphere resulted in significant motor improvements (Bundy et al., 2017). While not involving BCIs, another approach to bypass injured brain networks is through modification of peripheral nerve anatomy. Transfer of the C7 nerve root from the nonparalyzed side to the paralyzed side (28% had strokes) improved arm function compared to rehabilitation alone (Zheng et al., 2018).

Conclusion

In conclusion, the biology of recovery after stroke involves complex interrelated systems of neural repair. After a stroke, there are spontaneous changes in both structure and function within the brain. The future is optimistic, and several approaches to augment neural repair through pharmacological and neurotechnological means are under study. These include strategies that target both gray and white matter, including axon sprouting, dendritic branching, neurogenesis, axon preservation, remyelination, blood brain barrier integrity, blockade of extracellular inhibitory signals, alteration of excitability, and promotion of new brain cortical maps and networks.

Despite these many targets and promising preclinical data, progress has been more modest translating these interventions to augment neural repair in clinical trials. One fundamental hurdle to overcome lies in clinical trial design and appreciating the heterogeneity of stroke injury and repair; the right patient that stands to benefit must be selected for the right intervention at the right time point after stroke and the right outcome must be measured to determine efficacy. A second fundamental hurdle lies in our understanding the differences between preclinical models and human patients; the model brain's structure (such as less white matter in rodent brains) and function (such as different timing of changes in excitability) must be considered when translating findings into clinical trials. When evaluating interventions, there are principles that should be considered in any study, be it basic, translational, or clinical (Table 4). The Stroke Recovery and Rehabilitation Roundtable (SRRR) established new standards for stroke recovery and neural repair research: better understanding the natural history of recovery, increasing neurobiological data in human subjects, characterizing different stroke recovery phenotypes, training new researchers, developing a network of clinical centers, and promoting collaborative dialogue (Bernhardt et al., 2017). The SRRR also discussed strategies to enhance alignment between pre-clinical studies of neural repair and clinical trials of recovery (Corbett et al., 2017).

Importantly, the SRRR also suggested an approach to future clinical trials for rehabilitation and repair (Kwakkel et al., 2017). Future trials should incorporate standard definitions of recovery, patient characteristics (demographic, medical history, location/size of stroke, responders vs nonresponders), time points post stroke (enroll within 7 days and contain outcomes at least 3 months post stroke), and measured outcomes (NIH stroke scale for stroke severity, Fugl-Meyer for function and structure, Action Research Arm Test for upper limb, EQ-5D for quality of life, modified Rankin scale for global disability) (Kwakkel et al., 2017). Given stroke recovery is modality specific, we further recommend that trials employ modality-specific endpoints, in addition to global ones (Cramer, Koroshetz, & Finklestein, 2007). Having standardized approaches to trial design will facilitate multi-center trials, pooling of multiple studies, and aid meta-analyses. Momentum continues to grow with the accumulating understanding of the biology of neural repair. As thrombolysis changed stroke care in the 1990s and thrombectomy in the 2010s, the augmentation of neural repair for recovery after stroke may revolutionize care for these patients in the coming decade.

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Figure 1. Structural and functional changes in spontaneous neural repair after stroke.

A. Structural changes hypothesized to play a role in neural repair after gray matter and white matter stroke. Several processes are represented at the histologic level, including axon sprouting, dendritic branching, neurogenesis, axon preservation, remyelination, and glial scarring.

B. Functional changes hypothesized to play a role in neural repair through integrated mechanisms involving the whole brain. There are changes in excitability, brain cortical maps, and plasticity.

Table 1.

Hierarchical structural and functional changes in spontaneous neural repair after stroke. Neural repair is defined by these collective processes if they lead to functional recovery. A hierarchical framework can be helpful to understand these changes. Structural changes occur from the transcriptome (molecular program) level to the cell and tissue level. Functional changes occur from the excitability level to the cortical map and plasticity levels. The levels are often bidirectionally inter-related, whereby changes at one level induce changes at another. Further, structural changes can induce functional changes and vice versa.

Structural changes

Transcriptome: Molecular program of repair through gene expression

Mediators and pathways: Transcription factors, cytokines, chemokines, growth factors, and other molecules. Examples include:

Ang-1, BDNF, CCL2, CCR5, CREB, CSP, DLK, Ephrins, EPO, FGF-2, GAP43, G-CSF, GDF10, LIF, MAG, MCT-1, MOBP, NGF, NMNAT1, NogoA, SDF-1, Semaphorins, STAT3, TGFbeta, TLR3/TLR4, TNFalpha, VEGF

Cells: Neurons, astrocytes, oligodendrocytes, endothelial cells, pericytes, microglia, infiltrating inflammatory cells

Tissue: Gray versus white matter, infarct versus peri-infarct versus distant brain/cord, specific regions and nuclei

Changes result in axonal sprouting, dendritic branching, neurogenesis, axon preservation, remyelination, glial scar

Functional changes

Excitability: Acute excitotoxicity versus subacute pathologic inhibition

Enhance by: Increasing glutamate-AMPA, further decreasing phasic GABA (synaptic), decreasing tonic GABA (extrasynaptic)

Brain cortical maps and networks: Through macro-level changes and plasticity

Enhance by: Altering signaling to augment repair processes

Table 2.

Abbreviations and terms.

Abbreviation	Term	References
AMPA	Alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid	Clarkson et al., 2011; Carmichael, 2012
Ang II	Angiotensin II	Regenhardt, Bennion, & Summers, 2014
Ang-1	Angiopoietin-1	Ohab & Carmichael, 2008
BDNF	Brain-derived neurotrophic factor	Schabitz et al., 2004; Clarkson et al., 2015
cAMP	Cyclic adenosine monophosphate	Xu, Zhang, & O'Donnell, 2011
CCL2, MCP-1	Chemokine ligand 2, Monocyte chemoattractant protein-1	Kahle & Bix, 2013
CCR5	C-C chemokine receptor type 5	Joy, Zhou, Cai, Silva, & Carmichael, 2015; Joy et al., 2019
cGMP	Cyclic guanosine monophosphate	Xu, Zhang, & O'Donnell, 2011
CREB	cAMP response element-binding protein	Clarkson, Parker, Nilsson, Walker, & Gowing, 2015
CSPs	Chondroitin sulfate proteoglycans	Alia et al., 2016
DLK	Dual leucine zipper kinase	Hinman, 2014
EPO	Erythropoietin	Tsai et al., 2006; L. Wang, Zhang, Wang, Zhang, & Chopp, 2004
FGF-2	Fibroblast growth factor-2	Berry et al., 2005; Kawamata et al., 1997
GABA	Gamma aminobutyric acid	Clarkson, Huang, Macisaac, Mody, & Carmichael, 2010
GAP43	Growth associated protein 43	Overman et al., 2012
G-CSF	Granulocyte-colony stimulating factor	Schneider et al., 2007
GDF10	Growth differentiation factor 10	Li et al., 2015
LIF	Leukemia inhibitory factor	Davis et al., 2019
MAG	Myelin-associated glycoprotein	Cramer et al., 2013
MCT-1	Monocarboxylate transporter-1	Hinman, 2014; Rinholm et al., 2011
MOBP	Myelin-associated oligodendrocytic basic protein	Ward, 2017
NGF	Nerve growth factor	Krakauer, J.W., Carmichael, S.T., 2017
NgR1	Nogo receptor 1	Takase, Kurihara, Yokoyama, & Takei, 2017; Sozmen et al., 2016
NMNAT1	Nicotinamide mononucleotide adenylyltransferase 1	Hinman, 2014; Hinman et al., 2015
NogoA	Neurite outgrowth inhibitor A	Lindau et al., 2014
OPC	Oligodendrocyte progenitor cell	Shindo et al., 2016; Xiao & Hinman, 2016
PDE3	Phosphodiesterase-3	Krakauer, J.W., Carmichael, S.T., 2017
PDE4	Phosphodiesterase-4	MacDonald et al., 2007
PDE5	Phosphodiesterase-5	Krakauer, J.W., Carmichael, S.T., 2017

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Abbreviation	Term	References
SDF-1	Stromal cell-derived factor-1	Kahle & Bix, 2013
STAT3	Signal transducer and activator of transcription 3	Hinman, 2014
TGFbeta	Transforming growth factor beta	Krakauer,J.W., Carmichael,S.T., 2017
TLR4	Toll-like receptor 4	Hayakawa et al., 2016; Hayakawa et al., 2016
TNFalpha	Tumor necrosis factor alpha	Klassen et al., 2003
VEGF	Vascular endothelial growth factor	Z. G. Zhang et al., 2000

Table 3.

Potential targets to augment neural repair after stroke.

Target	Example
Gray matter	
Axonal sprouting	Inosine, PDE inhibitors, Growth factors, Stem cells
Dendritic branching	CCR5 blockade, Growth factors, Stem cells
Neurogenesis	Cerebrolysin, Growth factors, Stem cells
Angiogenesis	Growth factors, Stem cells
White matter	
Axon preservation	MCT-1 augmentation, NMNAT1/DLK/STAT3 manipulation
Remyelination	OPC proliferation/differentiation, Nogo blockade
Blood brain barrier	Endothelial cell metabolism, Pericyte proliferation
Microglia	TLR4 inhibition, Manipulating activation state
Glial scar	
Myelin-associated proteins	Nogo, MAG, MOBP blockade
Extracellular matrix proteins	Chondroitin sulfate proteoglycan inhibition
Growth cone inhibitors	Semaphorin, Ephrin blockade
Excitability	
Alter inhibition pharmacologically	SSRIs, CREB induction, GABA antagonism, Zolpidem, Amphetamines, L-dopa
Alter inhibition neurotechnologically	Transcranial magnetic stimulation, transcranial direct current stimulation, Deep brain stimulation, Vagal nerve stimulation
Brain cortical maps and networks	
<i>Macro level changes that depend may on changes in structure/excitability</i>	Rehabilitation: physical, occupational, speech Activity-based therapies, Sensory stimulation, Robot-based therapies Cognitive strategies, Functional MRI, Virtual reality Brain computer interfaces, C7 nerve root transfer

Table 4.

Recommendations for approaches to future basic, translational, and clinical studies (Bernhardt et al., 2017; Corbett et al., 2017; Kwakkel et al., 2017).

Overall Goals	Trial Considerations
Understand natural history of recovery	Use standard definitions of recovery
Collect neurobiological data in humans	Include patient characteristics:
Characterize stroke recovery phenotypes	<i>Demographics, medical history, location/size of stroke, responders vs nonresponders</i>
Organize network of clinical centers	Include time points post stroke:
Align preclinical and clinical studies:	<i>Enroll within 7 days and include outcomes at least 3 months post stroke</i>
<i>Appropriate animal models, tissue and behavioral outcomes</i>	Include time points post stroke:
Train new neural repair and stroke recovery researchers	<i>NIHSS (stroke severity), FM (function and structure), ARAT (upper limb), EQ-5D (quality of life), mRS (global disability)</i>